Safety and efficacy of biological DMARDs in elderly rheumatoid arthritis patients: staying the distance

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Running head: Biologics in elderly rheumatoid arthritis patients

Abstract

The population of elderly individuals with rheumatoid arthritis is rapidly expanding, mainly due to the increased life expectancy. While targeted biological therapies are well established for the treatment of this disease, their use may be lower in elderly (> of 65 years old) and very elderly patients (> 75 years old) due to perceived higher risks for adverse events in this population taking into account comorbidity, polypharmacy and frailty. In this review we discuss available evidence for the use of biological therapies in this growing patient group with specific attention towards eventual reasons for biological treatment failure or withdrawal. The majority of data is found in secondary analyses of clinical trials and in retrospective cohorts. Most information is available about tumor necrosis factor (TNF) blockers. Older patients seem to have a less robust response to anti-TNF agents than a younger population, but drug survival that may considered a proxy for efficacy does not seem to be influenced by age. Despite an overall rate of adverse effects comparable to that in younger patients, elderly RA patients are at higher risk of serious infections. Other biologics appear to have an efficacy similar to anti—TNF agents, also in the elderly RA patients. Again, the drug survival rates for tocilizumab, rituximab and abatacept resemble those in young RA patients with good general tolerability and safety profiles. The cardiovascular risk and the risk of cancer, increased in RA patents and in the elderly patients, do not appear to be strongly influenced by biologicals.

Key points

- Biological drugs targeting specific cytokines or immune cell populations are an important part of the management strategy for rheumatoid arthritis patients, including the elderly.

- Overall safety and tolerability in the elderly patients is very good and age should not be a critical factor to decide against biological drug use.
- The drug survival rate of biologicals in the elderly RA patients is comparable to that in the young RA population.
- Co-morbidities and risk of infection are important variables to assess when considering a biological drug in the elderly.
- More data and specific studies are required to better position biological drug use in this particular population as current studies provide a low level of evidence. Data in patients above 75 years are still largely missing. Moreover, the group of elderly patients that were included in clinical trials may be influenced by selection bias at inclusion and not be fully representative for infections risks and other comorbidities.

1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic auto-immune disease that is clinically characterized by symmetrical polyarthritis [1]. Current estimates suggest a disease prevalence of 0.5 to 1% of Caucasian populations, slightly less in Asian populations [2, 3] and overall more rare in Africans [4, 5]. Not only genetic but also environmental factors, including shorter life-span may play a role in such differences in prevalence. Women are about three times more affected then men. Peak age of onset for women is considered between 50 and 60 years whereas for men it is suggested to be over 70 years [6].

With the increased life expectancy and quality of life, the number of older patients with RA is steadily increasing in the Western world, representing 10-33% of all RA cases [7]. The overall prevalence of RA in older persons (≥60 years) is estimated around 2% and reaching up to 2.8% after 70 years [8].

The World Health Organization suggests to define an elderly person as having a chronological age of 65 years or above (WHO. Definition of an older or elderly person. www.who.int/healthinfo/survey/ageingdefnolder/en.). The use of calendar age to define an older individual is somewhat arbitrary, as it assumes equivalence with biological age. Aging in humans is however a complex dynamic and multidimensional process and cannot be denoted as a simple dot on a timeline. It correlates with changes in physical, social and psychological status and progressive functional decline. Gradual decrease in renal and hepatic function, diminished total body water and albumin levels, increased body fat contribute to many important changes including modifications in drug pharmacokinetics and pharmacodynamics [9]. Elderly patients with RA suffer more from comorbidities such as hypertension, diabetes mellitus, chronic obstructive pulmonary and cardiovascular disease

than younger patients [10], often resulting in polypharmacy and an increased risk of drug interactions. Specific geriatric conditions, such as cognitive impairment, depression, malnutrition, sensory limitations, mobility restrictions and incontinence result in decreased functional capacity and reduced ability to withstand or compensate for acute or chronic illness [11]. The concept of frailty is used to define an inevitable multifactorial progression toward functional decline. It involves multiple systems and manifests as wasting (weight loss and loss of muscle mass), decrease in performance (physical and cognitive), loss of endurance, inactivity and sensorial/physical impairment. Frailty leads to important vulnerability of older patients, higher risk of infections, falls, hospitalizations and mortality [12].

During aging, the highly sophisticated and finely tuned immune system undergoes marked changes, known as immunosenescence. This affects both the innate as well as the adaptive arms of the immune system and results in a decreased capacity to resolve infections, but also in pro-inflammatory changes and breaks in self-tolerance. The aging of the innate immune system leads to the dysregulation of dendritic cells (DCs), neutrophils, Natural Killer (NK) cells and macrophages with increased production of pro-inflammatory cytokines and higher circulating levels of TNF, IL-6, C-reactive protein (CRP) and other pro-inflammatory molecules, creating a pro-inflammatory environment [11, 13]; this process is described sometimes as “inflammaging” [14] .

The most striking changes probably take place in the adaptive immune system. With the thymic involution and, presumably, ageing of hematopoetic stem cells (HSC) due to reduced telomerase activity and shift in HSC subpopulations, the generation of new T cells progressively declines. The latest elicits compensatory proliferation of peripheral naïve and

memory T-cells, known as homeostatic proliferation [13]. The proportion of naïve regulatory T cells decreases with age, but their absolute numbers stay relatively stable as the proportion and the absolute numbers of memory T cells increase. Additionally, the total CD4+T cell counts significantly increase with age and CD8+T cell counts decrease, resulting in significantly raised CD4/CD8 ratio in elderly subjects [15]. Furthermore, both T cells subsets undergo changes in their receptor expression and thereby in their function. In a nutshell, the contracted T cell receptor (TCR) repertoire and loss of CD28, a pivotal co-stimulatory receptor necessary for T cell activation and proliferation, result in marked phenotypic changes. The CD4+CD28- cells may acquire NK-like functionalities [16], produce more pro-inflammatory cytokines and become resistant to apoptosis [17]. These cells are prone to react with self-antigens and it comes as no surprise that CD4+CD28- populations are increased in several auto-immune diseases, RA in particular [11]. The CD8+CD28- cells become unable to produce cytokines, but acquire the ability to suppress antigen-presenting function of DCs. Major repercussions of the aging of the immune system are an increased risk of infectious diseases, reduced response to vaccination and raised risk of cancer. The risk of autoreactivity, as discussed earlier, also increases with age and autoantibodies are more frequently detected in the elderly population [18].

The aim of this paper was to review and critically discuss the literature available for the use of biological therapies in the elderly (> 65 years) and very elderly (> 75 years) RA patients with specific attention towards eventual reasons for therapy failure or withdrawal. We also identify some important practical considerations for the use of biologics in this specific population.

2. Rheumatoid arthritis in the elderly

Interestingly, RA is characterized by accelerated signs of immunosenescence, regardless of disease duration or the age of onset [11]. Changes observed in the immune system of RA patients are similar to those in the elderly, leading ultimately to breach of self-tolerance. Just like in older individuals, telomere shortening in the lymphocytes [19], T-cell aging and emergence of CD28- cells are seen in RA patients [13]. But whether these changes suggesting immunosenescence are a cause or a consequence of RA is still unclear.

This raises the question whether there are differences between RA in young and elderly patients and whether these affect the management strategies? Generally, older patients have more comorbidities, cognitive impairment and present with geriatric syndromes due to age but also as a consequence of RA and its eventual treatment [20].

Functional disability also increases with advancing age [20] and longer disease duration [21-23]. In addition, female gender, high baseline disease activity, elderly onset, multiple comorbidities [21], especially cardiovascular disease, are also associated with disability and lower quality of life [24]. Impaired kidney and liver function and polypharmacy may also contribute to worse prognosis in the seniors with RA. These issues all make the assessment and the management of RA increasingly complex. Of note, depression in RA patients does not correlate with age [25] and contributes to functional disability [21].

Some intriguing studies are available comparing young- and elderly onset RA. Younger patents often have higher baseline disease activity with higher swollen joint count, acute onset and higher ESR and CRP levels [26]. The proportion of patients positive for characteristic auto-antibodies such as the rheumatoid factor and anti-citrullinated protein antibodies in this group is lower [27, 22]. Initially, they tend to have more radiographic

damage [28, 26], but radiographic progression itself appears independent of age [26, 28, 27]. More radiological damage and higher disease activity at baseline, as well as positive anti-CCP antibodies are predictors of radiological progression in early onset patients [29]. Older patients [29, 21], are less likely to achieve remission; female gender and higher baseline DAS28 lower their chances of achieving this clinical response [27]. Older patients also tend to have higher functional disability [24].

As discussed, the risk of infection increases with age but RA, especially when presenting with extraarticular manifestations, and its treatment also largely contribute to this risk. Moreover, patients residing in rural areas, with ≥ 2 comorbidities, chronic lung and renal disease and previous infection are particularly at risk [30]. Furthermore, RA doubles the risk for myocardial infarction and stroke, increasing death from cardiovascular disease by 30%. Although, the relative risk is highest in younger patients, the absolute rate is increased in older age categories [31], and cardiovascular problems are the number one cause of mortality in elderly RA patients [32]. Finally, patients with RA have an increased risk of cancer [33], especially Hodgkin's and non-Hodgkin lymphoma, non-melanoma skin cancer (NMSC) [34, 35] and possibly lung cancer [36]. The rate of colorectal and breast cancer however seems to be lower than in general population[33].

3. Treatment of elderly RA in the XXI century

Despite comparable and sometimes higher disease activity, some studies show that elderly RA patients receive less aggressive treatment [22, 37, 38]. This may be dependent on the local setting as according to others, the use of DMARDs is comparable in both young and old RA patients [23, 24]. The classic DMARD use varies from 12 to 97.3 % and decreases with age [37]. Combinations of synthetic DMARDs are also used less often [37, 38].

But is this always justified? As outlined, these patients have more comorbidities, polymedications, often impaired renal clearance and hepatic function. But independently, age considerations may erroneously result into automatically perceiving elderly patients as being frail and unable to tolerate the medications, and thus undertreating them [39].

Methotrexate is the DMARD of choice in half [40] to two thirds of elderly RA patients, but tolerability seems to be lower with about 30 to 50 % of patients experiencing adverse effects leading to treatment discontinuation [39]. This pivotal drug works in synergy with biologic agents, increasing their efficacy, and older patients receiving combination therapy (methotrexate and anti-TNF) have higher persistence than those on biologics monotherapy, with the strongest associations being observed for infliximab and adalimumab [41].

Glucocorticoid use in older patients is significantly higher than in younger patients with RA [23, 22, 38, 37, 29, 27, 42], but is not associated with achievement of low disease activity or remission [29, 43]. Furthermore, the risk of infection in elderly patients taking even low doses (equivalent of ≤ 5 mg of prednisolone) of glucocorticoids is notably higher than in those taking any synthetic DMARD and is twice as high as in those exposed to anti-TNF agent [30].

Despite fulfilling the treatment criteria, the biologics are used less frequently and older patients have to wait longer until such treatment is initiated [44]. However, the overall use of biologics in the elderly RA population is increasing [45]. The use of anti-TNF agents also decreases with age varying from 41 to 25% [39, 37, 45, 44], not exceeding 6% in octagenarians [38], according to some studies. The discontinuation rate is comparable to the young RA population with half of patients over 65 years stopping the treatment for various reasons (adverse effects and inefficacy) [43].

3.1 Anti-TNF α agents in older RA patients

Targeting the pro-inflammatory cytokine TNF has dramatically changed the treatment and outcome of patients with different auto-immune or auto-inflammatory disease, in particular those with RA. TNF is a cytokine produced by different cells types including macrophages and T cells that promotes synovial inflammation. Both soluble receptors (etanercept) as well as different antibodies (infliximab, adalimumab, golimumab and certolizumab pegol) have been developed as drugs. It is not surprising that the elderly population is largely underrepresented in the randomized control trials, achieving at best 12-22% in the RA study groups [46] Moreover, these patients are rarely stratified and little information is available about the "very elderly" (75 years and older) in particular**.** Retrospective analyses and data from patients subsets in clinical trial may suffer from selection bias. In particular, for clinical trials, patients with less comorbidities and low infection risk were probably selected.

Gradually more and more data on anti-TNF therapy in the senior RA population are appearing not only from clinical trials and their secondary analyses, but also from large prospective and retrospective cohort studies. Most of the information is available for etanercept, followed by infliximab and adalimumab. Practically no information is available on the "new" anti-TNFα agents: golimumab and certolizumab pegol in the elderly RA patients, most likely because these drugs were marketed much later than etanercept, infliximab and adalimumab.

3.1.1 Efficacy

Elderly patients seem to have a less robust response to anti-TNF therapy as compared to younger RA patients. However, head to head comparison with younger RA population is rare and only a few studies are available [28, 47, 48, 46] .

Several studies demonstrate that age may be a negative predictor of good response [43, 46] and remission [23]. Interestingly, according to the British cohort (BSRBR), the age and the baseline DAS28 are not predictive of response, while a lower baseline HAQ is predictive of remission [49]. Further, in a Dutch cohort (DREAM), the elderly patients had higher baseline disease activity and experienced less improvement in their disease activity scores with 20% less patients reaching good EULAR (European League against Rheumatism) response and remission criteria [50]. According to others, TNF-α blockers seem to be equally effective in the young, elderly and very elderly (≥ 75 years old) population on disease activity and radiographic progression, with best results seen in patients on combination therapy with methotrexate [47, 42, 28, 51].

Several *post hoc* analyses of late RA (LRA), early RA (ERA) and the TEMPO etanercept trials [52-55], evaluating its efficacy in the elderly [46, 48, 47, 56] demonstrated that older patients had similar or only slightly lower ACR responses, particularly the ERA group. Etanercept was equally effective on radiological progression in both groups [46]. Independently, the disease duration correlates with lower rates of ACR50 , ACR70 responses and remission [57].

Most studies suggest that improvement in physical functioning is less pronounced in the elderly, resulting in higher HAQ and worse functional outcome [42, 28, 51, 50]. In contrast, the secondary analysis of etanercept trials showed similar changes in the HAQ scores in both age groups, but the overall baseline and endpoint HAQ scores were higher in the elderly subjects [46]. As for the oldest geriatric subgroup (≥ 75 y.o.), they seem to have no functional improvement at all at the group level [42].

Finally, biologics treatment, in particular the use of anti-TNF therapy may have effects on the immunosenescence phenotype in RA discussed above. Anti-TNF-alpha in patients with RA seems to restore telomerase expression in T lymphocytes, thus delaying RA induced premature T senescence [58].

3.1.2.Tolerability and safety

Just like in young patients, anti-TNF therapy is usually well tolerated in the elderly. This translates into good but not optimal drug survival rates with some differences between specific products [43]. A recent meta-analysis confirms this data with drug discontinuation rate (for all the TF-alpha blockers pooled) gradually increasing over time and reaching 48-52% after 4 years of treatment. In this study the drug survival was highest for etanercept with only 40% discontinuation rate at 4 years. Of note, the age did not predict discontinuation for any causes, including adverse effects or a lack of efficacy. The disease duration did however predict a higher discontinuation for adverse effects [59]. According to the Swiss (SCQM-RA) and Dutch (DREAM) cohorts the drug discontinuation rates also appear to be similar in both young, elderly [42, 50] and very elderly (≥ 75 years) [42] with roughly quarter of patients stopping the treatment within the observation time. According to others however, the overall discontinuation rate is higher in senior patients and this is due to adverse effects, the efficacy being the same [60, 56, 51, 61]. Drug survival is an important proxy to assess drug efficacy and side effects. Interestingly, equivalent drug survival but lower drug response in elderly RA suggests that drug survival may be a good parameter to follow among elderly RA patients. Other confounding factors that could be monitored to prove biological safety and efficacy of biologics in this particular population are largely

missing (such as steroid decrease). Drug adherence is significantly higher in older patients concomitantly taking methotrexate [41, 46].

Pooled data from elderly patients with RA, psoriatic arthritis and spondyloarthritis treated with etanercept, revealed no difference in overall adverse effects with the young group (83.3 vs 77.1%), but the rate of serious adverse effects was higher in the elderly (29%, compared to 14.3 in aged ≤65 years). Interestingly, secondary analysis of the etanercept trials revealed slightly higher rate of adverse effects in the older patients, however comparable to the control groups [46].

Advanced age (≥ 80 years), diabetes mellitus and use of glucocorticoids are additional risk factors of adverse effects, in particular for infections. According to Iwanaga et al, the overall rate varied from 31.6% in all RA patients (treated with DMARDs and/or biologics) younger than 70 years old and reached 50% in the very elderly (≥ 80 years) [40].

Infection is effectively the most common relevant adverse effect of the anti-TNF therapy, most frequently being respiratory tract infections, especially pneumonia, herpes zoster and cellulitis [46, 40, 56, 30]. The overall rate of infections seems to be similar in the young and the elderly. But the rate of serious infections (requiring hospitalisation, IV antibiotics or resulting in death) is higher in the senior RA patients treated with these biologics [30, 56]. The incidence of serious infections is 20% higher in those exposed to anti-TNF agents, especially in the first 6 months of treatment, without significant difference between different molecules (infliximab/adalimumab/etanercept) [62]. According to another comparative study, the risk is threefold higher in the elderly RA patients. Even after adjusting for potential confounders, it is still higher for infliximab than for etanercept and is greatest 3 months after treatment initiation [63]. Schneeweiss et al however found no increased rate

of serious infections in the elderly RA patients treated with anti-TNF agents (infliximab/adalimumab/etanercept), after adjustment for other confounders including disease severity [64]. Although the TNF-α agents increase the incidence of infection, as mentioned earlier steroid exposure and previous infection are also important risk factors [30, 64, 65].

Herpes zoster infection (HZV) is one of the most common adverse effects in the elderly RA patients and deserves a special attention. Age and glucocorticoid use are independent risk factors for HZV infection [66, 67]. According to a retrospective cohort study based on Medicare insurance data, RA patients suffering from HZV infection were slightly older (mean age 67 vs 64 years) and more often used glucocorticoids. As for the biologics, the adjusted incidence rate of HZV was comparable for all the anti-TNF agents, albeit slightly higher for certolizumab [68]. The estimated rate in the senior patients is around 6.8% [40]. [66]

With regards to tuberculosis (TB), the patients included in RCTs after a screening for latent infection, did not seem to have a higher incidence than the control groups or general population [69, 70]. As for the elderly, no cases of TB were reported in the secondary analysis of etanercept trials [56, 46]. Another population-based study reported very low incidence of TB in the elderly patients with RA (0.05 event/1000 patient-years)[30].

As discussed earlier, rheumatoid arthritis is associated with higher risk for certain types of cancer, including lymphoma and non-melanoma skin cancer (NMSC). But do the TNF-blockers further increase this risk? This question was addressed in a large retrospective cohort study [71]. Anti-TNF therapy did not seem to increase the risk of lymphoma (any), solid tumors or NMSC in both primary and secondary analysis in young or the elderly (≥ 65), although the mean follow-up time was only 1 year. Again, in the secondary analysis of the

etanercept trials (LRA, ERA and TEMPO) the cancer rate in the older RA patients did not differ between the etanercept and control groups[56, 46, 61]. NSAIDs, glucocorticoid use and a history of solid or haematologic cancer are independent risk factors [35]. In the same cohort, cancer was the second cause of mortality (lung cancer followed by leukemia and non-Hodgkin lymphoma), and it was 50 % higher than in population controls [32].

Elderly RA patients have more cardiovascular comorbidities and a higher cardiovascular risk, compared to younger patients. The emerging picture on cardiovascular problems such as myocardial infarction and heart failure in patients treated with anti-TNF is not clear. The variable presence of comorbidities and risk factors in this population complicates the analysis. Only few studies addressing this interesting subject in the elderly RA patients are available, mostly retrospective cohort studies [72-75] . According to a recent publication, the patients treated with the anti-TNF-alpha agents (pooled data for adalimumab, certolizumab, etanercept, golimumab and infliximab) are at 28% higher risk of acute myocardial infarction (AMI), compared to those treated with abatacept but overall rates may be considered relatively low for the age group [72].

As for the heart failure in elderly RA patients, the role of TNF-alpha blockers remains uncertain. Of note, RA, independently of treatment strategies, is associated with higher risk of heart failure, higher disease activity and disease duration of more than 10 years being independent risk factors [76]. In a subgroup analysis Solomon et al showed that the heart failure risk in the elderly RA patients (>65 y.o.) treated with TNF-alpha antagonists was not increased and was even slightly lower compared to those treated with synthetic DMARDs (HR 0.75) [75]. According to Nurmohamed et al, every 6 months of anti-TNF treatment were associated with a 13% reduction of cardiovascular event risk in patients aged 50 years and

older, but elderly patients (> 65 y.o.) were underrepresented in this study (3.2%) [74]**.** In another study however, after adjustment for other confounders such as age, race and previous heart failure (HF), the TNF blockers were associated with the increased risk of hospitalization for the HF (HR 1.61) [73]. According to others, etanercept was not associated with the higher rates of cardiovascular events [61]. Most of these studies unequivocally mention glucocorticoids as an important dose-dependent risk factor for cardiovascular morbidity [72, 74, 75] , an observation that may influence treatment strategy decisions.

Demyelinating disorders have rarely been reported in patients treated with anti-TNF. In the post hoc analysis of several trials they were all seen in subjects aged ≤ 65 years [56, 61]. Thus, there is no clearly increased risk in the elderly population.

Although it is difficult to come up with a clear and undisputed conclusion, there is sufficient evidence to support the efficacy of anti-TNF strategies in elderly RA patients and to incorporate these strategies into a management plan for the disease that is no different from the approach in the younger patients, in particular taking into account that no specific safety concern has been identified that would be strongly different from what is to be expected in the population of interest.

3.2 "Other biologics", beneficial for the elderly with RA?

The treatment options for rheumatoid arthritis have dramatically changed over the last decade. Different potential targets have been identified and translated into therapeutic strategies that go beyond the first successful approach of inhibiting TNF. However, compared to the data that provide some insights into the use of anti-TNF agents in elderly patients, there is relatively little information available about the use of tocilizumab, rituximab and abatacept in the older RA population.

Despite their young age, these drugs established a solid ground in the treatment of rheumatoid arthritis and proved their efficacy and safety, comparable to the anti-TNF agents [77-80].

3.2.1. Tocilizumab

Tocilizumab is a humanized monoclonal antibody against the interleukin 6 (IL-6) receptor [77, 78, 81]. Not unexpectedly, most of the pivotal clinical trials included a majority of patients younger than 65 years. Tocilizumab seemed to be more effective in combination with methotrexate in young patients [81, 78]. In the elderly, the combination with methotrexate was not associated with greater treatment persistence [41].

The concept of blocking the IL-6 pathway in the older RA patients could provide a theoretical advantage, taking into account age-related pro-inflammatory changes, often higher baseline disease activity and higher CRP levels observed in the elderly [82, 83]. Surprisingly for this assumption, younger age seems to be predictive of good EULAR response [81]. Indeed, according to Pers et al. [84] a significantly smaller proportion of elderly RA patients has a good EULAR response (40.1% vs 61%). The moderate EULAR response as well as the drug survival were found similar in both age groups.

About half of the patients treated with tocilizumab experience some adverse effects [85, 78, 84], the most common being infections and allergic reactions. The most frequent serious infections are pneumonia and HZV, and the overall risk appears comparable to that seen with other biologics [10, 84, 86]. The elevation of liver enzymes, reduction in the neutrophil count and lipid changes (increase in levels of cholesterol and triglycerides) [87], specific to this particular drug [77, 78, 81], may be of concern in the elderly RA patients. However, compared to other biologics, the elderly patients treated with tocilizumab do not seem to

have an increased risk of myocardial infarction and even have a reduced risk of coronary heart disease outcome (myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting) [72]. Age, statin use, higher cholesterol levels and history of cardiac disorders, often encountered in seniors, are independent predictors of cardiovascular events in patients treated with tocilizumab [88]. An association was observed between the baseline total cholesterol:high-density lipoprotein cholesterol ratio and an increased risk of major adverse cardiovascular events. This risk while receiving treatment, however, was inversely associated with control of disease activity but not with lipid changes, suggesting indeed that better control of inflammation may at least partially offset an eventual increased risk due to drug-associated dyslipidemia [88]. No TB cases were observed in RCTs in patients treated with tocilizumab [69].

3.2.2. Rituximab

Rituximab is a cell-depleting anti-CD20 monoclonal antibody that specifically targets B cells without affecting the B lineage stem cell pool and the IgG producing plasma cells. The clinical trial and prospective cohorts included patients above 60 or 65 years but little attention has been paid to the elderly subgroups in the subsequent analyses. Nevertheless, there is some evidence that the proportion of good responders in the elderly and especially very elderly (≥ 75years) is significantly lower compared to younger patients. The improvement in DAS28 disease activity scores is significantly lower in the patients aged 75 years and older compared to patients between 65 and 75. However, in the same cohort discontinuation rates were not different between age groups [89]. In the German Gerinis cohort in contrast no difference in outcome were found between groups of patients younger and older than 60 years [90]. Similarly in this cohort, adverse events were not different between age groups.

Long-term analyses of the clinical trials and within real-life cohorts indicate that the withdrawal rate for this drug is relative low e.g just over 30% after two years in a large real-life cohort [89] and mainly occurring during the first two courses in around one-third of patients, irrespective of age (even in the very elderly, ≥ 75 years) [91]. Comparisons of drug survival among different biological agents is not easy as the administration interval may play a role in the patient's or physician's decision to stop a given treatment, but also in the recording and analysis of drug survival data. This is particularly the case with rituximab where intervals of treatment have been determined by reappearance of symptoms and of the target cells.

Tolerance and safety of rituximab in elderly patients with RA does not appear to be very different from that in younger patients. The most frequent adverse effects include infusion reactions and infections, predominantly of lower respiratory and genitourinary tract [91]. The rate of Herpes Zoster attacks is similar that seen with other biologics [86]. Just like for anti-TNF agents, some data suggest that severe infections are more frequent in the elderly (19.5%) and very elderly (26.5%), compared to less than 5% in the young subjects [89] but these data were not confirmed in the German cohort. Only two cases of TB were reported in the all-exposure population treated with rituximab in the clinical trial program [69]. Low IgG levels induced by or associated with the treatment, although rare (4%), are associated with higher rates of severe infection [91]. Also, no evidence of increased malignancy or cardiovascular risk has been reported in patients treated with rituximab [91]. Not unexpectedly and relevant for elderly patients, humoral responses towards pneumococcal and influenza vaccination are reduced in patients who receive rituximab. However, as concluded in a recent meta-analysis, vaccination still provides protection in a number of

cases and must be proposed to every RA patient, and the vaccination schedule should be adapted to the current or future treatment [92].

3.2.3. Abatacept

Abatacept or CTLA4-Ig is a selective modulator of T cell co-stimulation. Data about the use of abatacept in the elderly population with rheumatoid arthritis are scarce. Based on the limited available data sets age does not seem to influence the drug's effect on disease activity [93, 83].

According to a recent prospective cohort, remission, good and moderate responses are similar in young, elderly (65-74y.o.) and very elderly patients (>75 y.o.) at 12 and 24 months. Having a higher baseline activity, the very elderly had a lower probability of good response at 6 months, but at 12 months the difference was no longer statistically significant [83]. Drug survival rates from extension cohorts of the clinical trials and different cohorts under study indicate relatively low short term discontinuation rates [93-98]. Again, little information is available on the subpopulation of elderly patients. The age does not seem to influence the drug survival, with averagely tree-quarters of patients stopping their treatment at least once in a 24 month period in all age groups (<65 years, 64-74 years and ≥ 75 years) [83]. However, the discontinuation for lack of effectiveness decreases and discontinuation for adverse effects increases with age. Co-treatment with methotrexate does not appear to influence the treatment persistence in older patients based on a Medicare dataset based retrospective study [41].

Again, little specific safety data on the elderly patients is available in the literature. However, the EMA and FDA documents do report that the frequencies of serious infection and malignancy relative to placebo among abatacept-treated patients over age 65 in the clinical were higher than among those under age 65. The overall incidence of malignancies in the clinical development program of abatacept was not higher than expected in similar rheumatoid arthritis cohorts [99]. According to Lahaye, in patients treated with abatacept, the rate of adverse effects, especially serious infection increases with age [83], the most common infection sites being in bronchopulmonary, genitourinary systems and the joints. French real-life cohort study associated age and history of previous serious or recurrent infections with a higher risk of serious infections suggesting a hazard risk of 1.44 over 10 years for age [100]. The risk for herpes zoster flares was relative low with an absolute incidence rate of of 1.87 / 100 patient years [86]. The authors did not detect differences among different biologics. No cases of TB reactivation were reported for this drug. Of note, vaccination strategies may be more challenging in abatacept-treated patients. Combination of abatacept and a conventional DMARD significantly reduced the response towards the 2009 influenza vaccine [101]. Similar data have been proposed for vaccination against pneumococcus pneumoniae [102, 103].

Although abatacept appears an interesting option for elderly patients based on its safety profile and sustained benefit, it is clear that specific data are largely missing. Taking into account the working mechanism of this drug, further studies with additional translational analyses of the T cell repertoire and eventual changes induced by this molecule when treating elderly rheumatoid arthritis patients is of great interest. The prescribing information warning that patients over 65 should be better monitored for infection and malignancy does not appear to dictate a strategy that would be different than that for the other biologics

discussed in this review. The data on vaccines do not make vaccination in patients under treatment useless but do suggest that, whenever possible, the vaccination status of rheumatoid arthritis patients should be optimized before starting therapy with abatacept.

4. CONCLUSION

In conclusion, although elderly RA patients more often suffer from comorbidities and are at higher risk of infections and cardiovascular disease, they often have higher disease activity and functional disability. Unfortunately they are largely underrepresented in the clinical trials, often those with less comorbidities are selected. Older RA patients seem to have a less robust response to biologics and are less likely to achieve remission, but the treatment is generally well tolerated with withdrawal rates comparable to the young population. The drug survival rate is similar between different molecules and does not seem to be influenced by age. However, biologics are prescribed less and glucocorticoids more often in this group. The rate of adverse effects is similar to the younger RA patients, but the rate of serious adverse effects, especially serious infections, is higher in the elderly and especially very elderly. From this point of view, in light of latest research and current evolutions in clinical practice, tapering and stopping of biologicals in elderly patients in remission might be beneficial in reducing the adverse effects. To conclude, one should be cautious treating seniors with rheumatoid arthritis and meticulously evaluate the pros and the cons of the biologic treatment. However, the age alone should not limit our therapeutic options. As experience is growing the need of a true comparison between biologic DMARDs users in elderly and very elderly RA patients versus non-biologic users with matching procedures can be considered a priority.

Compliance with Ethical Standards:

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